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FEE TRANSMITTAL
For FY 2005**Complete if Known**

Application Number	10/623,891
Filing Date	July 21, 2003
First Named Inventor	Sanjay M. Reddy
Examiner Name	M. McGaw
Art Unit	1648
Attorney Docket No.	0167.03

☐ Applicant claims small entity status. See 37 CFR 1.27**TOTAL AMOUNT OF PAYMENT (\$) 500.00****METHOD OF PAYMENT** (check all that apply)☐ Check ☐ Credit Card ☐ Money Order ☐ None Other (please identify): _____☒ Deposit Account Deposit Account Number: 50-2132Deposit Account Name: **USDA-ARS-OTT**

For the above-identified deposit account, the Director is hereby authorized to: (check all that apply)

☒ Charge fee(s) indicated below☐ Charge fee(s) indicated below, except for the filing fee☒ Charge any additional fee(s) or underpayments of fee(s)
Under 37 CFR 1.16 and 1.17☒ Credit any overpayments**WARNING:** Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.**FEE CALCULATION****1. BASIC FILING, SEARCH, AND EXAMINATION FEES**

Application Type	FILING FEES		SEARCH FEES		EXAMINATION FEES		Fees Paid (\$)
	Fee (\$)	Fee (\$)	Fee (\$)	Fee (\$)	Fee (\$)	Fee (\$)	
Utility	300	150	500	250	200	100	-
Design	200	100	100	50	130	65	
Plant	200	100	300	150	160	80	
Reissue	300	150	500	250	600	300	
Provisional	200	100	0	0	0	0	

2. EXCESS CLAIM FEES

Small Entity

Fee Description	Fee (\$)	Fee (\$)
Each claim over 20 or, for Reissues, each claim over 20 and more than in the original patent	50	25
Each independent claim over 3 or, for Reissues, each independent claim more than in the original patent	200	100
Multiple dependent claims	360	180

Total Claims	Extra Claims	Fee (\$)	Fee Paid (\$)	Multiple Dependent Claims	Fee (\$)	Fee Paid (\$)
- 20 or HP =	x	=				

HP = highest number of total claims paid for, if greater than 20

Indep. Claims	Extra Claims	Fee (\$)	Fee Paid (\$)
- 3 or HP =	x	=	

HP = highest number of independent claims paid for, if greater than 3

3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper, the application size fee due is \$250 (\$125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

Total Sheets	Extra Sheets	Number of each additional 50 or fraction thereof	Fee (\$)	Fee Paid (\$)
- 100 =	/ 50 =	(round up to a whole number) x	=	

4. OTHER FEE(S)


Fees Paid (\$)

Non-English Specification, \$130 fee (no small entity discount)

Other: BRIEF ON APPEAL

\$500.00

SUBMITTED BY

Signature		Registration No. 34,078 (Attorney/Agent)	Telephone: (309) 681-6515
Name (Print/Type)	Randall E. Deck	Date	<u>5/9/05</u>

This collection of information is required by 37 CFR 1.136. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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P.C. 0167.03



PATENT

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

In re application of)
)
SANJAY M. REDDY ET AL.) Group Art Unit 1648
) Examiner M. McGaw
Marek's Disease Virus Vaccine)
)
Serial No. 10/623,891)
)
Filed July 21, 2003)

The Honorable
The Commissioner of Patents
Sir:

BRIEF ON APPEAL UNDER 37 CFR 1.192

This Appeal Brief is responsive to the final rejection of
claims 1-3, 5-10, and 12-15 in the above-identified U.S. patent
application.

I hereby certify that this correspondence is being deposited with the U.S.
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Signature

5/9/05
Date of Signature

05/13/2005 MAHME1 00000042 502132 10623891

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FEE PAYMENT

The Commissioner is authorized to charge the appeal brief fee of \$500.00 to Deposit Account No. 50-2132. Any delinquencies in fees may also be charged to deposit account no. 50-2132.

REAL PARTY IN INTEREST

The United States of America, as represented by the Secretary of Agriculture, is the real party in interest.

RELATED APPEALS AND INTERFERENCES

There are no appeals or interferences known to appellant, appellant's legal representative, or the assignee, which will directly affect or be directly affected by or have a bearing on the Board's decision in this appeal.

STATUS OF THE CLAIMS

Claims 1-3, 5-10, and 12-15 are now of record in this application. No claims have been allowed. Claims 4 and 11 have been cancelled, claims 1-3, 5-10, and 12-15 have been rejected. Claims 3, 5, 10, and 12 have been amended by the Amendment After Final Rejection submitted February 22, 2005. Claims 1-3, 5-10, and 12-15 are appealed.

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STATUS OF AMENDMENTS

An Amendment After Final Rejection was submitted on February 22, 2005, and was entered by the Examiner as indicated in the Advisory Action dated March 22, 2005.

SUMMARY OF INVENTION

The instant invention is drawn to appellants' discovery that an effective vaccine for Marek's disease may be prepared using a recombinant Marek's disease virus strain CVI988 transformed with a foreign DNA construct which includes a long terminal repeat sequence (LTR) of a reticuloendotheliosis virus (page 5, paragraph no. 0013, lines 1-5). This viral agent is effective to elicit a protective immune response in a chicken to Marek's disease virus without causing a significant degree of pathogenicity in the inoculated bird (page 13, paragraph no. 0053, lines 1-10). The recombinant Marek's disease virus of this invention may be prepared by transformation of any Marek's disease virus serotype 1 strain CVI988 or any of its clones or serially passaged strains, which are collectively referred to as strains CVI988/X (page 13, paragraph no. 0054, lines 1-4). This recombinant was first prepared using a pathogenic Marek's disease virus strain RM1 as the source of the reticuloendotheliosis virus LTR. The LTR was excised from the RM1 strain by digestion with

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the restriction enzyme *Pac* I, inserted into a vector, B40, and subsequently inserted into the desired Marek's disease virus strain CVI988 (pages 13-14, paragraph no. 0055, lines 1-16). Recombinant Marek's disease viruses having the LTRs integrated into their genome replicated faster than the parental CVI988 strain and were recovered and isolated. Appellants believe that this increased rate of replication is the result of the insertion of the reticuloendotheliosis virus LTR into the genome of the Marek's disease virus upstream of the ICP4 gene (page 14, paragraph no. 0055, last 7 lines). One of the resultant recombinant strains having the reticuloendotheliosis virus LTRs inserted therein, designated strain CVRM-2, was retained and deposited under the Budapest Treaty at the American Type Culture Collection, as deposit accession no. ATCC PTA-4945 (pages 6-7, paragraph no. 0020, and pages 20-21, paragraph no. 0070, lines 1-15). Recombinant Marek's disease virus containing reticuloendotheliosis virus LTRs may also be prepared from this deposited CVRM-2 strain by digestion of the DNA therefrom with *Pac* I restriction enzyme, inserting the resultant *Pac* I fragment into a vector, and transforming any Marek's disease virus strain CVI988/X strain therewith (page 15, paragraph 0057, lines 1-10).

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ISSUES

The issues for consideration as set forth in the Office actions are as follows:

- (1) Whether claims 1-3, 5-10, and 12-15 are unpatentable under 35 U.S.C. 103 as obvious over Witter *et al.* (1997) in view of Witter *et al.* (1995) and Jones *et al.* (1996).

GROUPING OF CLAIMS

The appealed claims do not stand or fall together, and claims 1, 2, 5-9, and 12-15 are separately patentable from claims 3 and 10. Accordingly, appellants request that the claims be considered as two groups as follows:

- (1) claims 1, 2, 5-9, and 12-15, and
- (2) claims 3 and 10.

The reasons why the claims are considered separately patentable are set forth in the "ARGUMENTS" section hereinbelow, as required by 37 CFR 1.192(c)(5) and MPEP 1206.

ARGUMENTS

Rejection Under 35 U.S.C. 103

Claims 1-3, 5-10, and 12-15 have been rejected under 35 U.S.C. 103 as being unpatentable over Witter *et al.* (1997) in

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view of Witter et al. (1995) and Jones et al. (1996). The Examiner has taken the position that it would have been obvious to substitute the CVI988/Rispens strain of Witter et al. (1995) for the JM/102W strain of Witter et al. (1997). The Examiner has also taken the position that Jones discloses the point of insertion of the LTRs. Appellants respectfully disagree.

Claim group 1, claims 1, 2, 5-9, and 12-15

Witter et al. (1997, hereinafter referred to as Witter '97) disclosed a recombinant Marek's disease virus, referred to as RM1, which had the long terminal repeats (LTRs) of a reticuloendotheliosis virus (REV) stably integrated into the repeat short (RS) regions of its genome. This strain was generated at the USDA-ARS-ADOL from a pathogenic serotype 1 Marek's disease virus, strain JM/102W, after co-cultivation with REV. Although the RM1 strain was shown to provide a level of protection similar or superior to that of CVI988, it was also associated with residual pathogenicity, and caused thymic atrophy in treated birds. The authors noted that the reason why the RM1 strain possessed these properties "cannot be definitively established" and speculated that there were several possible mechanisms for the activity of the RM1 strain, including the "possibility" that the insertion of the REV sequences caused a

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specific mutation in the Marek's disease virus genome (page 418, third paragraph). The authors concluded that the RM1 may provide a model for future vaccines, stating that:

"If the superior protection by RM1 clones derives from the selective attenuation of oncogenicity without influence on *in vivo* replication or other properties, then perhaps selective mutation of key genes will prove to be a useful strategy for developing superior serotype 1 vaccines" (emphasis added, see the paragraph bridging pages 419-420).

Witter et al. (1995, hereinafter referred to as Witter '95) disclosed the characteristics of two Marek's disease virus strains, CVI988/Rispens and R2/R3. The CVI988/Rispens strain was disclosed to provide improved disease protection with a reasonable degree of safety.

Jones et al. (1996, hereinafter referred to as Jones '96) further characterized the properties of the RM1 strain referred to in Witter '97, and disclosed that the LTRs were inserted upstream of the ICP4 gene.

The instant invention is drawn to appellants' discovery that an effective vaccine for Marek's disease may be prepared using a recombinant Marek's disease virus strain CVI988 transformed with a foreign DNA construct which includes a long terminal repeat sequence (LTR) of a reticuloendotheliosis virus. This viral agent is effective to elicit a protective immune response in a chicken to Marek's disease virus without causing a significant degree of pathogenicity in the inoculated bird. Recombinant

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Marek's disease viruses having the LTRs integrated into their genome replicated faster than the parental CVI988 strain and were recovered and isolated. Appellants believe that this increased rate of replication is the result of the insertion of the reticuloendotheliosis virus LTR into the genome of the Marek's disease virus upstream of the ICP4 gene (see the specification at page 14, paragraph no. 0055, last 5 lines). This is not disclosed or suggested in the prior art.

It is well established that the prior art must provide at least some predictability or a reasonable expectation of success to render a claimed invention obvious. See *In re Whiton* (CCPA 1970) 164 USPQ 455, *In re Rinehart* (CCPA 1976) 189 USPQ 143, and *In re Longhi* (CAFC 1985) 225 USPQ 645.

In the instant fact situation, although Witter '97 recognized the RM1 mutant virus provided a high level of protection against infection with Marek's disease virus, the authors readily admitted that the reason or mechanism for the increase in protection was unknown. It was not known if the effect was reproducible in other Marek's disease virus strains. Specifically, Witter '97 only suggested that "If the superior protection...derives from the selective attenuation of oncogenicity without influence on *in vivo* replication or other properties, then perhaps selective mutation of key genes will

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provide a useful strategy for development of superior serotype 1 vaccines" (emphasis added). Thus, there is no reasonable expectation of success.

The production of this single RM1 strain in Witter '97 is insufficient to establish any pattern or predictability linking the introduction of the LTRs into other Marek's disease virus strains, with increased vaccine efficacy. In other words, simply because one Marek's disease virus strain which has LTRs inserted into its genome exhibits increased efficacy, does not imply or suggest that all Marek's disease viruses transformed with LTRs will do the same. This is even more apparent considering the express acknowledgment by the primary reference that the result is uncertain.

At best, the prior art would only suggest that it would be obvious to try the substitution suggested by the Examiner. However, it is also well known that a rejection of obviousness under 35 U.S.C. 103 must be based on more than just a suggestion that it would be "obvious to try".

In addition to the comments above, appellants submit that even if the prior art provided the motivation to try to repeat the process of Witter '97 using another MDV such as CVI988, it would be highly unlikely that the process could be successfully repeated without the benefit of Applicants' invention. As

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disclosed in the specification at paragraph 0055 and recited in the claims, to be effective, the LTRs should be inserted upstream of the ICP4 gene of the Marek's disease virus. However, if a practitioner of ordinary skill in the art were to attempt to repeat the process of Witter '97 using a different Marek's disease virus strain, the LTRs could be inserted at numerous locations in the genome of the virus. This point of insertion would vary and could not be controlled. The skilled practitioner would have no reasonable expectation of success that the LTRs would be inserted at the correct position. It is only by virtue of Applicants' invention that the point of insertion can be controlled and LTRs can be introduced into other Marek's disease viruses to produce effective vaccines.

The other reference relied upon, Witter '95 and Jones '96, do nothing to compensate for the deficiencies of Witter '97. Witter '95 merely discloses the desirable properties of the CVI988/Rispens vaccine strain. It does not disclose or suggest inserting LTRs into the genome of CVI988, much less provide any guidance how that may be effected. Although Jones '97 does disclose the location of the LTR's insertion and its relation to the ICP4 gene, the reference only discloses that:

"since a potential promoter for the long form of the MDV ICP4 gene is located 100 to 200 bp upstream from the LTR insertion site (20b), it is conceivable that the ICP4

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transactivator may also be associated with the novel phenotype of RM1" (emphasis added).

As with Witter '97, this disclosure that a "potential" ICP4 promoter is upstream from the LTR insertion site and that "it is conceivable" that the ICP4 transactivator may be significant, does not provide a reasonable expectation of success, and at best, only suggests that it would be reasonable to try insertion of the LTRs at that location. Moreover, the reference provides no guidance how the site of insertion could be controlled to ensure insertion of an LTR at that location.

The unpredictability of repeating the process of Witter '97 using other virus strains is even more apparent in view of the disclosure of Parcells et al. [2004, Insertion of the LTR from reticuloendotheliosis virus (REV) upstream of SORF2 does not necessarily confer the phenotype associated with the RM1 strain of MDV, Abstract presented at the 7th International Marek's Disease Symposium, July 10-14, 2004, St. Catherine's College, Oxford, UK, a copy of which is enclosed herewith]. In brief, the authors attempted to do just what the Examiner has suggested: to insert the LTRs into the genome of Marek's disease virus strain CVI-988 at the same location that the LTRs were inserted into the RM1 strain (the same as that reported by Witter '97). However, despite their efforts, the authors reported that the resultant transformants containing the inserted LTRs did not exhibit

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enhanced replication. This failure clearly demonstrates that there would be no predictability or reasonable expectation of success in repeating the process of Witter '97 as suggested by the Examiner.

Appellants note that the above-mentioned Parcels abstract was presented in July, 2004, nearly one year after the filing date of the instant application, and therefore does not qualify as prior art under 35 U.S.C. 102.

In addressing Parcels, the Examiner appears to allege that because Parcels was published after the filing date, it would be unknown to practitioners skilled in the art, and thus a practitioner skilled in the art "could not be daunted by unknown obstacles" (page 8 of the final rejection). However, appellants have not suggested that Parcels would teach the skilled practitioner away from the invention. In contrast, what appellants have argued is that Parcels clearly illustrates the unpredictability of repeating the process of Witter '97 with other Marek's disease virus strains. Indeed, this should be even more apparent considering that other practitioners skilled in the art were unsuccessful although they had the benefits of several years of scientific advances after the publication of Witter '97, and even after appellants' filing date.

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Finally, appellants have also noted that the Examiner has alleged that the Parcells disclosure is sufficient to "bolster the notion that one would be motivated to do this and have a reasonable expectation of success" (page 9 of the final rejection). In reply, Parcells is not available as prior art under any section of 35 U.S.C. 102/103 and therefore cannot be relied upon to provide motivation for combining the references as suggested. As to the expectation of success, appellants note that the authors were not successful in arriving at applicants' claimed invention.

Claim group 2, claims 3 and 10

In addition to the arguments presented above, appellants believe that dependent claims 3 and 10 further differentiate over the prior art of record. As noted above, claims 3 and 10 recite process limitations describing that the long terminal repeat of the independent claims "comprises a *Pac I* excised DNA segment from Marek's disease virus strain ATCC PTA-4945." This is not disclosed or suggested in the prior art of record.

Even if the prior art did suggest inserting an LTR from a reticuloendotheliosis virus into a Marek's Disease virus as proposed by the Examiner (a point which is not conceded by appellants for the reasons noted), the prior art certainly

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provides no teaching whatsoever how that should be done. It is only by virtue of appellants' disclosure that a practitioner of ordinary skill in the art would excise the LTR from appellants' deposited strain using *Pac*I restriction sites as claimed.

CONCLUSION

For the reasons stated above, claims 1-3, 5-10, and 12-15 are believed to distinguish over the prior art of record. Allowance of all claims is respectfully requested.

Respectfully submitted,



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Peoria, IL

309/681-6515

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Enclosures

-Parcells et al. [2004, Insertion of the LTR from reticuloendotheliosis virus (REV) upstream of SORF2 does not necessarily confer the phenotype associated with the RM1 strain of MDV, Abstract presented at the 7th International Marek's Disease Symposium, July 10-14, 2004, St. Catherine's College, Oxford, UK, 2 pages]

APPENDIX

1. A viral agent comprising a recombinant Marek's disease virus CVI988/X stably transformed with a foreign DNA construct which comprises a long terminal repeat sequence of a reticuloendotheliosis virus, wherein said viral agent is effective to elicit an immune response in a chicken to Marek's disease virus without causing a significant degree of pathogenicity in said chicken, and further wherein said long terminal repeat sequence is inserted upstream of the ICP4 gene of said Marek's disease virus.

2. The viral agent of claim 1 wherein said long terminal repeat sequence comprises Sequence ID No. 2.

3. The viral agent of claim 1 wherein said long terminal repeat sequence comprises a *Pac I* excised DNA segment from Marek's disease virus strain ATCC PTA-4945.

4. (canceled).

5. The viral agent of claim 1 comprising Marek's disease virus strain ATCC PTA-4945.

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6. The viral agent of claim 1 wherein said recombinant Marek's disease virus is viable.

7. The viral agent of claim 1 wherein said Marek's disease virus is cell associated.

8. A vaccine comprising the viral agent of claim 1 in an amount effective to elicit a protective immune response in a chicken to Marek's disease virus and a pharmaceutically acceptable carrier or diluent.

9. A method for protecting a chicken against Marek's disease comprising inoculating said chicken with a vaccine comprising a viral agent in an amount effective to elicit a protective immune response in a chicken to Marek's disease virus and a pharmaceutically acceptable carrier or diluent, wherein said viral agent comprises a recombinant Marek's disease virus CVI988/X transformed with a foreign DNA construct which comprises a long terminal repeat sequence of a reticuloendotheliosis virus and said long terminal repeat is inserted upstream of the ICP4 gene of said Marek's disease virus, and further wherein said viral agent is effective to elicit a protective immune

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response in a chicken to Marek's disease virus without causing a significant degree of pathogenicity in said chicken.

10. The method of claim 9 wherein said long terminal repeat sequence comprises a *Pac I* excised DNA segment from Marek's disease virus strain ATCC PTA-4945.

11. (canceled).

12. The method of claim 9 wherein said viral agent comprises Marek's disease virus strain ATCC PTA-4945.

13. The method of claim 9 wherein said viral agent is viable.

14. The method of claim 9 wherein said vaccine is cell associated.

15. A method of making a viral agent effective for protecting a chicken against Marek's disease comprising transforming a Marek's disease virus strain CVI988 with a foreign DNA construct which comprises a long terminal repeat sequence of a reticuloendotheliosis virus, and further wherein said long

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terminal repeat is inserted upstream of the ICP4 gene of said
Marek's disease virus.

PLENARY SESSION III

Virulence and Virus Evolution

III.2

Insertion of the LTR from reticuloendotheliosis virus (REV) upstream of SORF2 does not necessarily confer the phenotype associated with the RM1 strain of MDV

Parcells, M.S.¹, Y. Wu², R. L. Dienglewicz¹, P. M. Kumar¹, N. Pritchard³, & M. Buñblot⁴

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The insertional mutagenesis of the MDV genome by retroviruses (ALV, REV) has provided unique insight into a possible mechanism of herpesvirus evolution. The isolation of the RM1 virus, from a highly-attenuated strain of MDV (JM-102) passaged with reticuloendotheliosis virus (REV) chicken syncytial virus (CSV) and found to have enhanced replication *in vivo*, was very supportive of this concept. Characterization of RM1, which contained an insertion of a truncated LTR within the repeats flanking the unique short region (IRs and TRs), showed an increased level of transcription across the SORF2 gene. As RM1, unlike JM-102 at similar passage level, induced thymic atrophy, was non-oncogenic when inoculated into one day-old chickens and provided complete protection against vv+MDV, there was a strong correlation of the LTR insertion and this phenotype. To replicate this finding and determine if this insertion alone could confer enhanced replication of MDV, a vaccine strain (CVI-988) was sequentially constructed to contain the insertion of the LTR sequence from RM1 at the identical location within the IRs. This recombinant MDV was constructed via incorporation of the LTR adjacent to a loxP site-flanked GFP expression cassette (loxP-CMV-lacsmGFP-polyA-loxP). Recombinant MDVs were screened according to GFP expression and the isolated recombinant DNA was treated with Cre recombinase *in vitro*. Non-fluorescent MDVs were then isolated and plaque purified. We were able to generate both GFP+ and GFP- viruses containing the LTR from RM1 inserted in either orientation at the specific locus. Interestingly, no dual insertions were noted in stocks of these viruses and the recombinants contained insertions in only the IRs, but not the TRs region of the genomes. Characterization of the parental, GFP+ and GFP- viruses showed that the recombinants did not replicate *in vivo* to the same level as the parent virus. Stocks of the viruses reisolated from birds showed that the A orientation recombinants (same LTR orientation as RM1) were stable after *in vivo* replication, yet the GFP- B orientation recombinant was not. In no instance was duplication of the insertion at both repeats noted. The inability of the RM1-like LTR insertion in a CVI-988 background to confer enhanced replication *in vivo* may be due to slight differences of the insert sequence (Lox site), or insertion in only one of the two inverted repeats. Mutations other than the LTR insertion within the IRs/TRs may also contribute to the enhanced replication of RM1.

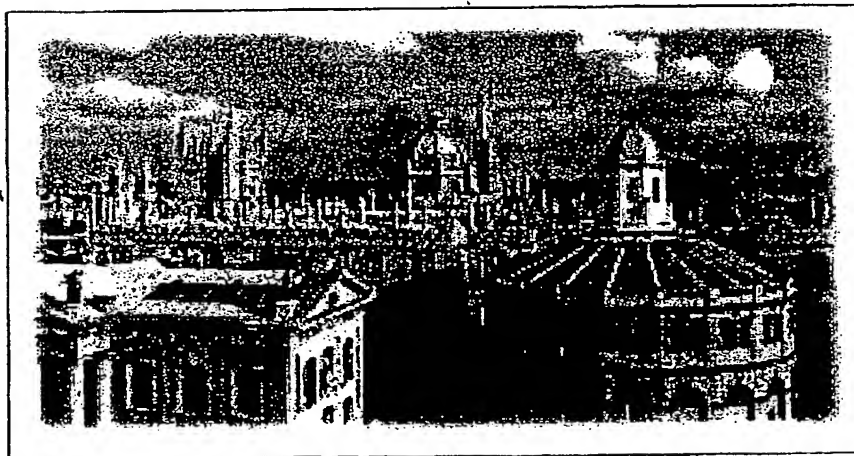
Notes:

p22 CVI CVI-1 CVI-2
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